

Exploration of health dimensions to be included in multi-attribute health-utility assessment

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Abstract

Objective. Measurement of health utility is important for quality improvement, but instruments vary in their content. Multi-attribute health utility measures typically assess a small number of health problems, e.g. the EuroQoL EQ-5D questionnaire explores five dimensions of health. We aimed to examine whether a small number of dimensions explains a sufficient amount of variance in self-perceived health, and what can be gained from adding additional dimensions.

Design. Cross-sectional mail survey that explored health utility and self-perceived health.

Setting. General resident population of French-speaking Switzerland.

Participants. Non-institutionalized adults.

Main outcome measures. EQ-5D (which measures mobility, self-care, usual activities, pain/discomfort, anxiety/depression and a visual analogue health scale between 0 and 100 (VAS)). A subsample rated five additional health dimensions (sleep, memory/concentration, energy/fatigue, sight/hearing, contacts with others).

Results. In total, 349 adults returned the extended 10-item questionnaire. All added items were strongly and significantly associated with the VAS for perceived health. The proportion of variance explained (R^2) in the VAS was 0.47 for the original EQ-5D items (adjusted for attenuation: 0.65), 0.47 for the new items (adjusted for attenuation: 0.65) and 0.56 for the 10 items together (adjusted for attenuation: 0.78). Forty-four percent of the respondents who had a perfect health utility on the EQ-5D reported at least one problem in the new health dimensions.

Conclusion. Self-perceived health among the general public is influenced by more health dimensions than are typically measured in a multi-attribute health-utility instrument.

Keywords: health utility, outcome assessment (health care), quality indicators, health care, health surveys, models, statistical

Introduction

Patient outcomes measures are an important part of quality improvement. Among them, health-utility measures are particularly useful because they allow comparisons of health interventions across disease groups, and are required for economic analyses. Health utility, the value attributed to a given health state, can be measured directly by preference-based methods, such as the standard gamble or the time trade-off, or approximated by multi-attribute instruments, such as the EQ-5D [1, 2], the Health Utilities Index (HUI) [3, 4] and the SF-6D [5]. The latter identify the level of function or ability in several dimensions of health, and map these

health states onto a health-utility scale established by preference-based methods.

To be usable such instruments typically probe only a handful of health dimensions. Inevitably, unmeasured dimensions of health cannot influence the utility assessment, so that all utilities will be incorrect to some extent. This would not be a problem if the distribution of utility losses by health dimension obeyed the Pareto principle—i.e. if a small number of health problems explained the majority of the utility losses in a population. However, this assumption is largely unproven. On the contrary, available evidence suggests that this assumption may be wrong. Indeed, existing multi-attribute instruments vary in the dimensions they

measure (Table 1), and health utilities obtained with different instruments agree only moderately [6–11].

To explore this issue further we considered the EQ-5D, the most widely used multi-attribute health-utility instrument (a recent standardized Medline search retrieved 1004 articles for EQ-5D, 147 for HUI and 122 for SF-6D). However, the question of how many dimensions are necessary is not specific to this instrument, but concerns the multi-attribute measurement strategy in general. EQ-5D measures five dimensions of health—mobility, self-care, usual activities, pain and discomfort and anxiety or depression. Substantial proportions of the general population obtain ‘perfect’ health-utility values on the EQ-5D, yet these respondents vary in their self-assessment of health on the EQ-5D visual analogue scale (VAS), or as captured by other health status indicators [12–16]. This suggests that EQ-5D may omit relevant dimensions of health. Of note, an early version of the instrument included an item for fatigue and tiredness [17], and two previous studies tested an item for cognitive performance [18, 19], but no study has explored the consequences of including a broader set of health dimensions.

Assessing the contributions of additional dimensions to health utility is potentially daunting. The EQ-5D describes 243 distinct health states, but doubling the number of items would yield 59 049 health states. A valuation task for even a small fraction of this many health states would be challenging. To avoid this difficulty, we analysed self-perception of health instead of health utility. While these concepts differ—health utility depends on values and preferences associated with health states, unlike general health perception—we assumed that it would be unlikely that a health problem should affect health utility but not self-perception of health, and vice versa.

Table 1 Comparison of dimensions of health assessed in health-utility questionnaires

EQ-5D	SF-6D	HUI 2	HUI 3
Mobility	Physical functioning	Mobility	Ambulation
Self-care		Self-care	
Usual activities	Role limitations		
Pain/discomfort	Pain	Pain	Pain
Depression/anxiety	Mental health	Emotion	Emotion
	Social functioning		
	Vitality		
		Sensation	Vision, hearing, speech ^a
		Cognition	Cognition
		Fertility	
			Dexterity

^aSeparate dimensions.

In this study, we aimed to determine how much variance in self-perceived health would be explained by the 5 original dimensions of the EQ-5D, by 5 additional health dimensions and by all 10 dimensions used together.

Methods

Study design

We conducted a general population mail survey in French-speaking Switzerland [12]. To measure health utility, the majority of the participants completed the standard EQ-5D, including the five dimension-specific items—mobility, self-care, usual activities, pain and discomfort, anxiety and depression—and the ‘thermometer’ VAS that measures self-perceived health. A randomly selected subset completed an expanded version, in which five additional dimensions were added—sleep, memory and concentration, energy and fatigue, sight and hearing and contacts with others. We selected these additional dimensions based on a review of existing health-utility instruments [3–5] and general health status questionnaires [20–28]. Sleep is included in the Duke Health Profile (DHP) [20], the Nottingham Health Profile (NHP) [21], the Sickness Impact Profile (SIP) [22] and the World Health Organization Quality of Life Scale (WHOQOL) [23]. Cognitive ability is measured by the DHP, HUI, WHOQOL and the Medical Outcome Study HIV questionnaire (MOS-HIV) [24]. Energy and fatigue are measured by the SF-6D, NHP, the Quality of Life Index [25], the Short-Form 36 [26] and WHOQOL. Vision and hearing are included in the HUI, the McMaster Health Index Questionnaire [27] and SIP. Social contacts are assessed by the SF-6D, the Short-Form 36, the COOP Charts for Primary Care Practice [28], DHP, NHP, SIP and WHOQOL.

Study variables

The questionnaire began with the measure of health utility, the EQ-5D in its original form, or expanded to 10 items. This was followed by a question asking whether the previous items addressed all important aspects of the respondent’s health (answers were yes, completely, yes, in part, no), and an open question about what dimensions of health were missing (answers to this open question are not analysed in this paper). Further items included current health status on a 5-point scale between poor and excellent, current treatment for a chronic or acute health problem, doctor visit in past 6 months, hospital stay in past 6 months, sex, age, country of birth and highest education.

Data collection

Data collection was conducted by an independent survey firm (Infometrics, Le Muids, Switzerland) which had up to date lists of residents of the selected cantons. This firm selected the random sample of adult residents (20 years or older), mailed the survey packages, collected the numbered

returned questionnaires, sent out reminder packages (up to two reminders to non-respondents), performed data entry and transmitted the anonymous data file to the investigators. The survey package included a cover letter, the questionnaire booklet and a prepaid return envelope. The letter explained the purpose of the study, identified study investigators (with telephone number) and survey firm, described confidentiality procedures and stated that participation was voluntary. To signify consent to participate, the respondent was asked to return the completed questionnaire, and to signify refusal, to send back the questionnaire empty, in which case no reminders were sent. The study was approved by the research ethics committee at the University Hospitals of Geneva.

Sample size estimation

The primary purpose of the survey was to obtain population norms for EQ-5D [12], for which the target sample size was 1645. Allowing for 10% of invalid addresses and a response rate of 45%, a simple random sample of 4000 individuals was initially contacted. Of these, 3250 received the standard version of EQ-5D, and 750 received the 10-item version, to insure that at least 300 respondents would have completed the 10-item questionnaire.

Statistical analysis

We compared the subsamples who answered the standard EQ-5D and the extended 10-item version. We examined the distributions of the EQ-5D items and the five additional items, and computed mean values of the VAS across levels of problems for each item.

To examine the independent contributions of problems in the health dimensions to self-perceived health, we used two types of analyses. First, we used a linear regression model with the health VAS as the dependent variable, and obtained the proportion of variance in health explained by health problems (adjusted R^2). The health problems were treated as linear covariates, because the limited sample size posed difficulties in estimating the effects of severe problems for most dimensions. We corrected the R^2 results for the attenuation caused by imperfect measurements [29], assuming reliability coefficients of 0.80 for the health VAS and 0.90 for the linear combination of health dimensions. For simplicity, we displayed regression coefficients (i.e. differences in VAS) for the absence versus presence of a problem, combining moderate and severe problems.

Second, we used logistic regression with the rating of health ('excellent' or 'very good' versus 'good', 'fair' or 'poor', which resulted in two groups of similar size) as the dependent variable, and obtained the area under the receiver operating characteristic curve (ROC). These analyses were conducted on the total sample (for the original 5 dimensions only), and on the subsample who completed the extended questionnaire, comparing the models with 5 original dimensions, 5 new dimensions and all 10 dimensions. The analysis of variance explained was repeated in various population subgroups.

To explore the ceiling effect of the EQ-5D, we examined frequencies of problems on the new dimensions among respondent who achieved maximum scores on the original instrument. Then, we compared those who reported no problems on any of the 10 dimensions with those who reported problems on the new dimensions only, in terms of acute or chronic health problems, doctor visits or hospitalizations in the previous 6 months. Analyses were performed using SPSS software, version 17.

Results

Study sample

After exclusion of 253 invalid addresses (undeliverable mail), 3747 persons remained eligible (3047 in the original EQ-5D group, 700 for the extended version) and 1952 returned the questionnaire (52.1%); 1603 the standard EQ-5D questionnaire and 349 the extended version. The response rate was higher for the standard questionnaire than for the extended questionnaire (52.6 vs. 49.9%, $P = 0.19$), and for women compared with men (56.5 vs. 46.7%, $P < 0.001$).

Among the 349 respondents who answered the extended questionnaire, 181 were women (51.9%), and the mean age was 50.6 years [standard deviation (SD) 16.5]. The majority was born in Switzerland (74.1%), had received only elementary or vocational education (60.5%), and reported a doctor visit in the past 6 months (76.4%), but few had been hospitalized (8.5%). Acute and chronic health problems were reported by 13.0 and 34.8% of respondents, respectively, and 47.6% rated their health as excellent or very good. The mean VAS health score was 80.9 (SD 14.6).

Health problems

Among respondents who filled in all 10 health dimensions, most reported no problems with mobility, self-care or usual activities, but problems with pain or discomfort (48.2%) and with anxiety or depression (34.2%) were quite common (Table 2). Of the five new dimensions, the most frequent source of complaints was fatigue/energy (52.5%), but problems with sleep (36.8%), memory and concentration (35.6%) and with seeing or hearing (28.5%) were also common. In contrast, only few (7.0%) reported problems in contacts with others.

All 10 problems were strongly and significantly associated with the mean rating of health on the VAS (Table 2). Taking as an example the most common problem in the original EQ-5D, the mean VAS score was 84.7 in respondents who were not anxious or depressed, 74.8 in those moderately anxious or depressed and 53.4 in those who were extremely anxious or depressed. For the most common problem among the new items (tiredness and lack of energy), the gradient in the mean VAS for the three response categories was 88.1, 76.4 and 53.0.

Correlations between the newly proposed dimensions and the original dimensions of EQ-5D were weak to moderate

Table 2 Distributions of the five EQ-5D items and of the five additional items among 349 adult residents of French-speaking Switzerland, and association with VAS (thermometer)

EQ-5D original dimensions	<i>n</i> (%)	Mean VAS (SD)
Mobility (three missing)		($P < 0.001$)
I have no problems in walking about	310 (89.6)	83.3 (12.2)
I have some problems in walking about	36 (10.4)	58.4 (16.9)
I am confined to bed	0 (0)	—
Self-care (four missing)		($P < 0.001$)
I have no problems with self-care	338 (98.0)	81.6 (13.7)
I have some problems washing or dressing myself	7 (2.0)	48.2 (19.2)
I am unable to wash or dress myself	0 (0)	—
Usual activities (three missing)		($P < 0.001$)
I have no problems with performing my usual activities	311 (89.9)	84.5 (11.7)
I have some problems with performing my usual activities	32 (9.2)	57.9 (17.3)
I am unable to perform my usual activities	3 (0.9)	52.0 (24.0)
Pain/discomfort (five missing)		($P < 0.001$)
I have no pain or discomfort	178 (51.7)	87.4 (10.2)
I have moderate pain or discomfort	159 (45.6)	74.8 (14.2)
I have extreme pain or discomfort	9 (2.6)	53.4 (23.7)
Anxiety/depression (four missing)		($P < 0.001$)
I am not anxious or depressed	225 (65.2)	84.7 (11.0)
I am moderately anxious or depressed	114 (33.0)	75.6 (15.6)
I am extremely anxious or depressed	6 (1.2)	40.7 (18.0)
Additional dimensions		
Sleep (one missing)		($P < 0.001$)
I have no problems with sleep	220 (63.2)	85.1 (11.9)
I have moderate difficulties with sleep	111 (31.9)	76.3 (13.5)
I have extreme difficulties with sleep	17 (4.9)	56.0 (19.9)
Memory/concentration (one missing)		($P < 0.001$)
I have no problems with memory or concentration	224 (64.4)	85.5 (10.8)
I have moderate difficulties with memory or concentration	120 (34.5)	73.8 (15.9)
I have extreme difficulties with memory or concentration	4 (1.1)	47.2 (18.1)
Fatigue/energy (two missing)		($P < 0.001$)
I feel full of pep	165 (47.6)	88.1 (9.4)
I am moderately tired or lacking in energy	164 (47.3)	76.4 (12.9)
I am extremely tired or lacking in energy	18 (5.2)	53.0 (20.4)
Seeing and hearing (with glasses, contact lenses or hearing aid if you have them) (six missing)		($P < 0.001$)
I see and hear without difficulty	245 (71.4)	83.3 (11.3)
I have moderate difficulties seeing or hearing	91 (26.5)	72.6 (16.5)
I have extreme difficulties seeing or hearing	7 (2.0)	64.2 (31.4)
Contacts with others (two missing)		($P < 0.001$)
I have very good contacts with my family and friends	323 (93.1)	82.4 (12.7)
I lack contact with my family and friends	21 (6.1)	67.0 (18.8)
I am completely isolated from my family and friends	3 (0.9)	50.0 (36.1)

(mean 0.28, SD 0.11, range 0.11–0.48). This was similar to correlations among the original 5 dimensions (mean 0.29, SD 0.13, range 0.11–0.54).

Prediction of global health from dimension-specific problems

In multivariate linear regression analysis, problems in all five EQ-5D dimensions were significantly associated with the

VAS health rating (Table 3). The adjusted R^2 of the model was 0.46 among all respondents and 0.47 among those who filled the extended version of the questionnaire. Among the latter subsample, if only the five new health problems were used as predictors, the adjusted R^2 of the model was 0.47, same as for the original EQ-5D items. The predicted health scores obtained from the original EQ-5D dimensions and from the new dimensions had a correlation of 0.70, i.e. a shared variance of 0.49. Inclusion of all 10 items yielded an

Table 3 Linear regression models relating absence of problems in health dimensions to VAS health rating (thermometer)

Predictors in model	Full sample ($n = 1845$ with complete data)		Subset who rated 10 dimensions ($n = 333$ with complete data)			
	Original 5 predictors		5 predictors (separate models for EQ-5D and new dimensions)		All 10 predictors	
Absence of problem ^a in:	Difference	<i>P</i> value	Difference	<i>P</i> value	Difference	<i>P</i> value
Mobility (EQ-5D)	9.7	<0.001	10.3	<0.001	7.1	0.002
Self-care (EQ-5D)	13.4	<0.001	14.8	0.003	11.2	0.033
Usual activities (EQ-5D)	15.2	<0.001	11.8	<0.001	10.1	<0.001
Pain/discomfort (EQ-5D)	8.1	<0.001	8.8	<0.001	4.9	<0.001
Anxiety/depression (EQ-5D)	6.0	<0.001	4.5	<0.001	0.5	0.69
Sleep (new)			5.6	<0.001	3.7	0.003
Memory/concentration (new)			4.7	0.001	3.3	0.009
Fatigue/energy (new)			8.5	<0.001	5.2	<0.001
Sight/hearing (new)			7.2	<0.001	4.2	0.001
Contacts with others (new)			10.5	<0.001	6.4	0.007

^aCompared with moderate or severe problem.

Table 4 Variance in perceived health status explained by the original 5 EQ-5D dimensions, the new 5 dimensions and all 10 dimensions, overall and in population subgroups

	Adjusted R^2 (R^2 corrected for attenuation)		
	EQ-5D dimensions	New 5 dimensions	All 10 dimensions
Overall	0.47 (0.65)	0.47 (0.65)	0.56 (0.78)
Sex			
Women	0.53 (0.74)	0.48 (0.67)	0.60 (0.83)
Men	0.40 (0.56)	0.49 (0.68)	0.53 (0.74)
Age (years)			
20–59	0.48 (0.67)	0.44 (0.61)	0.54 (0.75)
≥ 60	0.45 (0.63)	0.45 (0.63)	0.54 (0.75)
Country of birth			
Switzerland	0.44 (0.61)	0.42 (0.58)	0.54 (0.75)
Other	0.48 (0.67)	0.56 (0.78)	0.60 (0.83)
Highest schooling completed			
Basic ^a	0.52 (0.72)	0.53 (0.74)	0.60 (0.83)
Advanced ^b	0.33 (0.46)	0.29 (0.40)	0.41 (0.57)
Chronic health problem			
No	0.31 (0.43)	0.29 (0.40)	0.41 (0.57)
Yes	0.38 (0.53)	0.48 (0.67)	0.52 (0.72)

^aElementary or vocational.

^bBaccalaureate, professional school or university.

adjusted R^2 of 0.56 (R^2 change: 0.09, $P < 0.001$). In the final model, the effect of anxiety/depression virtually disappeared (regression coefficient near zero) and became non-significant (Table 3). Correction for attenuation by imperfect reliability increased the observed R^2 coefficients from 0.47 to 0.65, and from 0.56 to 0.78 (Table 4).

Assessment of the variance explained was repeated in various population subgroups (Table 4). The original dimensions explained more variance in health among women than among men. The variance explained was lower among the Swiss than among foreign-born respondents, and particularly among the more educated and those who did not report any chronic health problem.

We used the rating of health as ‘excellent’ or ‘very good’ as opposed to ‘good’, ‘fair’ or ‘poor’ as the dependent variable in a logistic regression model. Using problems on the 5 standard EQ-5D dimensions as predictors, the area under the ROC curve was 0.79 ($P < 0.001$), both in the full sample and in the subset who responded on 10 health dimensions. Using the new five dimensions, the area under the curve was 0.82 ($P < 0.001$). When all 10 problems were included in the model, the area under the ROC curve improved to 0.86 ($P < 0.001$).

Ceiling effect

In the sample that completed the extended version of the questionnaire, 40.2% reported no problems in the original EQ-5D dimensions (Table 5). In this subgroup (and excluding 3 respondents who had missing values on the additional health dimensions), 59 respondents had at least one problem in one of the added dimensions, leaving 75 with no problem in the 10 dimensions of the extended questionnaire. Comparisons of other health-related variables confirmed that the additional health dimensions did identify sicker individuals among those who reported no problems on the original EQ-5D.

Discussion

This study suggests that a utility measurement instrument that is limited to five dimensions of health will miss

Table 5 Analysis of the ceiling effect of the EQ-5D

	Respondents with highest utility on EQ-5D			<i>P</i> value
	All (<i>n</i> = 137)	Below EQ-10D ceiling (<i>n</i> = 59) ^a	At EQ-10D ceiling (<i>n</i> = 75) ^a	
Problem with sleep	16 (11.7)			
Problem with memory/concentration	23 (16.8)			
Problem with fatigue/energy	33 (24.3)			
Problem with sight/hearing	16 (11.9)			
Problem with contacts with others	2 (1.5)			
Acute health problem	5 (3.8)	4 (7.0)	1 (1.4)	0.17
Chronic health problem	14 (10.4)	11 (19.3)	3 (4.1)	0.008
Doctor visit in past 6 months	66 (50.8)	35 (63.6)	30 (42.3)	0.014
Hospitalization in past 6 months	2 (1.5)	2 (3.6)	0 (0)	0.19
Self-reported health 'excellent' or 'very good'	95 (74.8)	33 (61.1)	62 (84.9)	0.002
Health VAS, mean (SD)	88.8 (8.6)	85.8 (8.9)	90.8 (7.8)	0.001

^aFour missing values.

important health problems in a large proportion of members of the general public. Furthermore, five alternative health dimensions that were identified through literature review were just as able to explain self-perceived health as the original EQ-5D dimensions. Inclusion of all 10 items improved the proportion of variance in self-perceived health that can be explained by specific health issues.

The newly proposed items identified problems that were common in this population. More than half of the respondents reported feeling tired or lacking in energy, more than a third reported problems with sleep and with memory or concentration and more than a quarter had problems seeing or hearing. Only 'contacts with others' revealed problems in less than 10% of the respondents. Omitting these dimensions (with the possible exception of 'contacts with others') from multi-attribute health-utility instruments entails a substantial loss of information.

Furthermore, the proportion of variance explained in self-perceived health (measured by the thermometer VAS) was identical for the original EQ-5D items and the five new items. It seems that the original dimensions of EQ-5D are not particularly fundamental to explaining differences in health. This observation calls in question the content validity of currently available multi-attribute instruments, and the methods by which health dimensions are selected for inclusion. Further work may be needed to identify the dimensions of health that cause most losses of health utility. It may be that these dimensions will vary with the population of interest—e.g. general population studies may require a different set of dimensions than specific patient groups. For instance, in our data, the EQ-5D dimensions explained a larger part of variance in health among women than among men, which was not the case for the new dimensions.

Once the most relevant health dimensions are identified or ranked in order of importance, a difficult decision is to decide how many should be included. Practical considerations dictate as few as possible, but measurement

requirements call for some criterion of comprehensiveness, such as the proportion of variance in health explained by the instrument. While there are no universal rules for interpreting R^2 statistics, we would consider that 0.47 of variance explained (or 0.65 after correction for attenuation) is insufficient if the predictors (the health problems) are used as proxies of the dependent variable (health utility), and if the results of such analyses are to guide health policy decisions or patient care. However, on this point opinions may differ.

Our results provide a realistic estimate of the improvement that can be achieved by increasing the number of dimensions of health-utility instruments. By adding five dimensions, the proportion of variance explained went from 0.47 to 0.56 (or from 0.65 to 0.78 after correcting for attenuation) and the area under the ROC curve in predicting excellent or very good health increased from 0.79 to 0.86. We would consider that a substantial improvement, but whether it is sufficient remains debatable. Furthermore, we are aware of the practical difficulties. Increasing the number of dimensions entails a substantial cost, by making the valuation procedures using preference-based methods exponentially more complex. An alternative possibility is that a smaller subset of health dimensions can be identified that would explain a sufficiently large part of the variance in health and health utility. Possibly, a different subset would be needed for different subgroups of the population.

In choosing the relevant health dimensions, content validity is an important concern. In this study, we did not define health, but relied instead on the respondents' lay definitions. Clearly the developers of multi-attribute health-utility instruments are entitled to their own definitions, and these differ across instruments. For instance, HUI developers aimed to measure only (potential) function, not actual performance [4], arguing that the latter depends also on opportunities and choices made by the individual. In contrast, authors of EQ-5D and SF-6D were interested in actual performance in daily life. Choosing the right conceptual framework for health is a key decision in health-utility measurement, and yet this

issue has been subjected to little debate thus far. Consensus in this area would facilitate the selection of the most relevant health dimensions for measurement.

This study has several limitations. We have explored self-perceived health, not the *value* attributed to one's health. It may be reasonable to assume that health problems that influence the perception of health would also influence the willingness to trade time for health improvement, but it does not necessarily follow that the strength of the associations would be similar. For example, people may be more willing to trade life expectancy for relief from pain than for relief from fatigue. Secondly, our study tested only five new dimensions of health. While their choice seemed reasonable based on the available literature, the list is by no means closed. In fact, at the outset we hoped to identify one or two health dimensions that would improve the performance of the existing instrument, and did not expect to discover that the selection of relevant dimensions was such an open question. In view of our results, a more thorough exploration of health dimensions that affect health utility, using a larger sample, would be in order. Finally, the response rate of 50% raises the risk of selection bias, such as the healthy volunteer effect. However, we believe that selection bias is less likely to affect associations between variables, the focus of our study.

This study suggests that self-perceived health among the general public is influenced by more health dimensions than are typically measured in a multi-attribute health-utility instrument. Devising a brief but sufficiently comprehensive instrument is a challenge for the science of health-utility assessment.

Authors' contributions

T.P. conceived the study, obtained funding, supervised data collection, analysed the data, and wrote the paper. D.C. discussed data analysis methods, interpreted the results and revised the paper. Both authors approved the final version of the paper.

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